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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
12/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,144	CHANG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,32-36,45 and 62-65* is/are pending in the application.

4a) Of the above claim(s) *33 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,32,34,36,45 and 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-1-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 10-1-07 has been entered. Claims 1-18, 32, 34, 36 and 45 have been amended. Claims 62-65 have been added. Claims 19-31, 37-44 and 46-61 have been canceled. Claims 1-18, 32-36, 45 and 62-65 are pending. Claims 1-18, 32, 34, 36, 45 and 62-65 are under consideration.

Election/Restrictions

1. This application contains claims 33 and 35 drawn to an invention nonelected with traverse in the reply filed on 3-15-07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 62-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants' amendment filed on 10-1-07 necessitates this new ground of rejection.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 62-65 are directed to a virus-ligand complex consisting of a cell-targeting ligand non-covalently bound directly to said virus, wherein introduction of said virus-ligand complex into a host animal would result in direct binding of the ligand directly to a receptor on the target cell, and a method of preparing said virus-ligand complex comprising mixing said cell-targeting ligand with said virus in a cell-free aqueous medium.

The specification teaches mixing Holo-transferrin with Ad5LacZ and the mixture is incubated at room temperature to produce virus-ligand complex (e.g. Example 1). The

specification fails to provide adequate guidance and evidence for how to produce a virus-ligand complex **consisting of** a cell-targeting ligand non-covalently bound to said virus, i.e. without any cell-free aqueous medium. The virus-ligand complex produced by the claimed method of mixing the ligand with a virus in a cell-free aqueous medium would still contain said aqueous medium. The specification fails to provide specific guidance for how to remove the cell-free aqueous medium. Further, the specification also fails to provide specific guidance and evidence for how to administer a virus-ligand complex **consisting of** a cell-targeting ligand non-covalently bound to a virus, and said ligand bind directly to a receptor on said target cell in vivo. A virus-ligand complex **consisting of** a cell-targeting ligand non-covalently bound to a virus would be like a powder and it is unclear how to administer a powder to a host animal via various administration routes such that said ligand could binds directly to a receptor on the target cell in vivo. Absent specific guidance, one skilled in the art at the time of the invention would not know how to make and use a virus-ligand complex **consisting of** a cell-targeting ligand non-covalently bound to a virus.

For the reasons set forth above, it would have required undue experimentation for one skilled in the art at the time of the invention to make and/or use the full scope of the invention claims. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of skill which is high, the amount of experimentation required, and the breadth of the claims.

4. Claims 17, 18, 45, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment filed on 10-1-07 necessitates this new ground of rejection.

The phrase "mixing said cell-targeting ligand with said virus in a cell-free aqueous medium" in claim 17 and 64 is considered new matter. The specification only provide a few examples of mixing a ligand with a virus in a buffer solution, however, the specification fails to provide sufficient disclosure to support the phrase "mixing said cell-targeting ligand with said virus in a cell-free aqueous medium". Mixing a ligand with a virus in a buffer solution only represents a small portion of mixing in a cell-free aqueous medium and it does not encompass mixing a ligand with a virus in a cell-free aqueous medium. It does not exclude mixing a ligand with a virus in an aqueous medium in the presence of cell. The specification fails to provide sufficient disclosure to support the "cell-free medium". Therefore, the phrase set forth above is considered new mater. Claims 18 and 45 depend from claim 17. Claim 65 depends from claim 64.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 2, 6, 8-10, 12, 15-18, 32 and 45 remain rejected and newly added claims 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Cotten et al., 1992 (PNAS, USA, Vol. 89, pp. 6094-6098) and is repeated for the reasons set forth in the preceding Official action mailed 4-30-07. Applicant's arguments filed 10-1-07 have been fully considered but they are not persuasive.

Applicants argue that the meaning of "non-covalent bond" is different from the meaning of "not covalently bound", and cite Figure 1 of Cotton, which teaches that the transferrin and polylysine complex and the adenovirus are added separately to the cell, and further argue that Cotton does not disclose ligand non-covalently bound directly to a virus (amendment, p. 19-20). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07. Cotten teaches mixing a plasmid DNA expressing luciferase under the control of RSV promoter with human or mouse transferrin-polylysine (equivalent to 4ug of polylysine) and the mixed solution is further mixed with a replication-defective human adenovirus 5 lacking functional E1a sequence (e.g. p. 6095, left column, 3rd paragraph, right column, 3rd paragraph). Cotten further teaches mixing the mouse transferrin-polylysine (mTfpL) with 10 ul of adenovirus dI312 containing $5x10^{11}$ particles/ml (e.g. Figure 3). The diagram in Figure 1 only demonstrates the different binding of transferrin-polylysine complex and adenovirus to the cell surface, it does not necessarily mean that the transferrin-polylysine complex and the adenovirus do not form complex. Figure 5 also shows that cell incubation mixtures include the hTfpL/DNA complexes and the adenovirus dI312. The instant invention teaches mixing the transferrin with a virus to produce the non-covalently bound complex, therefore, the mixing of hTfpL/DNA complex with the adenovirus dI312 as taught by Cotton would also be able to produce non-covalently bound

ligand-virus complex. The phrase "not covalently bound" in the Official action mailed 4-30-07 was meant to be "non-covalently bound".

Applicants argue that Cotton does not disclose each and every element of the claimed invention, specifically a virus-ligand complex comprising a cell-targeting ligand non-covalently bound directly to a virus (amendment, p. 21). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07 and the reasons set forth above.

Applicants argue that Cotton teaches administering the transferrin-polylysine conjugate and the adenovirus particles separately to the cells and even there is a complex formed between the conjugate and the adenovirus, it would be formed in the presence of cells (amendment, p. 21). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07 and the reasons set forth above. As discussed above, the phrase "mixing said cell-targeting ligand with said virus in a cell-free aqueous medium" in claim 17 and 64 is considered new matter, the specification fails to provide sufficient disclosure for said phrase. Even if the phrase is not new mater, the mixture of the transferrin-polylysine and the adenovirus could be considered cell free because the cells are in a monolayer on a dish rather than a suspension of cells.

7. Claims 1, 2, 6, 9-11, 15-18, 32, 45 remain rejected and newly added claims 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Seth et al., 1984 (Journal of Virology, Vol. 51, No. 3, p. 650-655) and is repeated for the reasons set forth in the preceding Official action mailed 4-30-07. Applicant's arguments filed 10-1-07 have been fully considered but they are not persuasive.

Applicants argue that Seth does not disclose a virus-ligand complex where a cell-targeting ligand is non-covalently bound directly to a virus. The exotoxin-EGF and adenovirus are administered to KB cells separately. Applicants further argue that since the PE-EGF hybrid toxin is not covalently bound to the adenovirus, therefore, there is no bond at all between the PE-EGF and the adenovirus (amendment, p. 22-23). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07. Seth teaches preparation of recombinant PE-EGF (Pseudomonas exotoxin and epidermal growth factor) hybrid toxin and mixing adenovirus and PE-EGF in 1.5 ml of fresh medium. "[T]hen 1.5 ml of fresh medium was added containing either adenovirus (o.1 to 10 ug/ml) or PE-EGF (0.01 to 0.5 ug/ml) or **both** (e.g. p. 650, right column 3rd full paragraph). It is apparent that adenovirus and PE-EGF are mixed before adding to cells and they can form complex having non-covalent bound before having contact with cells. As discussed above, the instant invention teaches mixing the transferrin with a virus to produce the non-covalently bound complex, therefore, the mixing of PE-EGF and the adenovirus as taught by Seth would also be able to produce non-covalently bound ligand-virus complex. The phrase "not covalently bound" means there is no covalent bond and it does NOT mean there is no bond at all because there are different bindings other than covalent bond.

Applicants argue that the PE-EGF-adenovirus complex is formed in the presence of cells and not formed in a cell-free aqueous medium as claimed (amendment, p. 23). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07 and the reasons set forth above.

8. Claims 1-12, 17, 18, 32, 34 and 45 remain rejected and newly added claims 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Spooner et al., 1994 (WO 94/10323) and is repeated for the reasons set forth in the preceding Official action mailed 4-30-07. Applicant's arguments filed 10-1-07 have been fully considered but they are not persuasive.

Applicants argue that Spooner only discloses chemical conjugation of a binding moiety to a polypeptide on the surface of the virus and not formation of a non-covalent bond between a cell-targeting ligand and a virus, and the reference O'Sullivan cited by Spooner discloses covalent conjugation via two different chemical methods (amendment, p. 23-25). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07. Spooner teaches the binding moiety polypeptide may be linked to the polypeptide on the surface of the virus or virus-like particle by any of the conventional ways of cross-linking polypeptides. Spooner just provides a few examples of cross-linking but it does not exclude non-covalent binding between the polypeptide and the virus or VLP.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 13 and 14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over either Cotten et al., 1992 (PNAS, USA, Vol. 89, pp. 6094-6098) or Seth et al., 1984 (Journal of Virology, Vol. 51, No. 3, p. 650-655) and is repeated for the reasons set forth in the preceding Official action mailed 4-30-07. Applicant's arguments filed 10-1-07 have been fully considered but they are not persuasive.

Applicants reiterate arguments regarding Cotton and Seth set forth above under 35 U.S.C. 102(b) rejection (amendment, p. 27-28). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07 and the reasons set forth above.

12. Claims 1 and 36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Spooner et al., 1994 (WO 94/10323) in view of Kingsman et al., 1997 (WO 97/32026) and is repeated for the reasons set forth in the preceding Official action mailed 4-30-07. Applicant's arguments filed 10-1-07 have been fully considered but they are not persuasive.

Applicants reiterates the argument regarding Spooner and argue that the complex between an adapter molecule and a virus particle as taught by Kingsman would form in the presence of cells and only after the adapter molecule is attached to the target cells. Applicants further argue that the ligand in the complex as taught by Kingsman would not bind directly to a receptor on the target cell when the complex is introduced into a host animal. Kingsman requires

the use of an unmodified ectropic vector rather than a modified vector as claimed in the instant invention (amendment, p. 29-31). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-30-07 and the reasons set forth above. The claims are product claims, therefore, whether the ligand could bind directly to a receptor on the target cells when introduced into a host animal is irrelevant. Kinsman teaches molecular adaptor molecules for targeting viral particles, in particular retroviral particles, to cells, a retroviral particle having molecular adapter molecules for gene therapy and for targeting retroviral delivery vector to specific target cells. Since the adaptor molecule is intended to target retroviral particles to cells, it would be apparent that the adaptor molecules and the retroviral particles would form a complex, such that the adaptor molecule can direct the retroviral particle to target cells, although they may not be administered at the same time, and it would be inherent that the ligand would bind to directly to the receptor on the target cells. Further, since the adaptor molecule is used to direct the retroviral particle to cells for gene therapy, it would be obvious that the retroviral particle would be modified to comprise a therapeutic nucleic acid. Thus, the claims remain rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.